

**REMARKS**

Reconsideration of this application is respectfully requested. Claims 12-15 and 17-20 have been canceled. Cancellation of these claims should not be construed as an acquiescence to any of the rejections and Applicants reserve the right to pursue these claims in a continuation application(s). Claims 1-11 and 16 are pending. Claims 1-11 and 16 have been amended. Support for amended claim 1 can be found at page 5, lines 5-9 and page 6, lines 5-8.

Applicants submit herewith a substitute Sequence Listing which contains SEQ ID NO:8. SEQ ID NO:8 represents the mature trichosanthin protein and is identical to amino acids 1-247 of Figure 1. The specification has also been amended to refer to SEQ ID NO:8.

Applicants respectfully submit that no new matter has been added by the present amendments. The issues raised by the Examiner are summarized and addressed below.

**Objections to the Specification**

The Abstract has been objected to because of the word "etc." in the third sentence. Applicants have amended the Abstract to remove this word, thereby rendering this objection moot.

The specification was also objected to because the Examiner contended that a specific priority reference to the earlier filed application was not included. Applicants have inserted the appropriate priority information. Therefore, Applicants respectfully submit that the objection to the specification can be withdrawn.

The Examiner also objected to the specification at page 3, lines 6-8. In particular, the Examiner contends that the phrase "remains strong positive" is unclear.

Applicants respectfully submit that the sentence is clear. However, in an effort to expedite prosecution, Applicants have amended the sentence to delete the term "positive." Accordingly, the sentence at page 3, lines 6-8 now reads "[t]his dysfunctional immune response to TCS usually

remains strong in the recipient's body for many years." Applicants respectfully submit that the phrase "remains strong" refers to the dysfunctional immune response. Therefore, Applicants respectfully request that the objection to the specification be reconsidered and withdrawn.

The Examiner has objected to the specification because of the word "etc." at page 5, line 25 and at page 12, line 12. Applicants have amended the specification to remove the word "etc." thereby rendering this objection moot.

The Examiner also contends that the sentence at page 15, lines 11-14 is unclear and questions whether the deletion of 5 amino acid residues has no effect on RIP activity.

Applicants respectfully submit that the deletion of 5 amino acid residues referred to in the specification at page 15, lines 11-14 has no effect on RIP activity. Applicants submit that this sentence is clear when considered in context of Applicants' specification. Therefore, Applicants respectfully request that the objection to the specification be reconsidered and withdrawn.

The Examiner has objected to the specification because of a typographical error in the word "inventors" at page 15, line 16. Applicants have amended the specification to correct the typographical error, thereby rendering this objection to the specification moot.

#### **Rejections under 35 U.S.C. § 112, Second Paragraph**

The Examiner has rejected claims 1-11 and 16 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner is of the opinion that "in claim 1, it is not clear what the mutant trichosanthin protein amino acid sequence encompasses, since the native trichosanthin protein does not have a reference sequence disclosed."

Applicants respectfully submit that claim 1 is clear and definite. However, in an effort to expedite prosecution, and in no way acquiescing to the Examiner's rejection, Applicants respectfully submit that claim 1 has been amended to specifically refer to SEQ ID NO:8, having modification of at least one amino acid residue in the following three regions: amino acid residues 174 to 180, 203 to 226, and 230 to 244, as the mutant trichosanthin (MTCS) protein. Applicants submit herewith a substitute Sequence Listing containing SEQ ID NO:8. SEQ ID NO:8 represents the mature trichosanthin protein and is identical to amino acids 1-247 of Figure 1. Applicants have also amended the specification to refer to SEQ ID NO:8. As amended, claim 1 clearly refers to SEQ ID NO:8 as the reference sequence of the trichosanthin protein. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Claim 1 has also been rejected under 35 U.S.C. §112, second paragraph due to the recitation of the phrase "low antigenicity."

Applicants respectfully submit that claim 1 is clear and definite. However, in an effort to expedite prosecution, and in no way acquiescing to the Examiner's rejection, Applicants have amended claim 1 to delete the phrase "low antigenicity." Accordingly, this rejection has been rendered moot.

Claim 1 has also been rejected under 35 U.S.C. §112, second paragraph, because, according to the Examiner, the term "substantially" is a relative term which renders the claim indefinite.

Applicants respectfully submit that claim 1 is clear and definite. However, in an effort to expedite prosecution, and in no way acquiescing to the Examiner's rejection, Applicants have amended claim 1 to delete the phrase "substantially retaining the biological activities." Accordingly, the rejection has been rendered moot.

Claim 1 has also been rejected under 35 U.S.C. §112, second paragraph, because, according to the Examiner, the metes and bounds of the phrase "biological activities" are not clear.

Deletion of the phrase “biological activities” in claim 1 has rendered the rejection moot.

Claim 1 has also been rejected under 35 U.S.C. §112, second paragraph, because the Examiner questions the meaning of the term “modification.” This rejection is respectfully traversed and reconsideration is respectfully requested.

Applicants respectfully submit that claim 1 is clear and definite in view of the teachings of Applicants’ specification. Claim 1, as amended, is directed to a mutant trichosanthin (MTCS) protein, comprising the amino acid sequence as set forth in SEQ ID NO:8, with the modification of at least one amino acid residue in the following three regions: amino acid residues 174 to 180, 203 to 226, and 230 to 244. The term “modification” is defined at page 6, lines 10-22 of the specification as follows:

[a]s used in this application, the term "modification" of amino acid residue refers to the deletion, insertion, addition, replacement, or chemical modification. In a preferred embodiment, the modification of amino acid residue causes a change in the electric charge of the amino acid site where the same modification is being made. The term "replacement" of amino acid residue preferably refers to replacing a hydrophilic amino acid residue with a hydrophobic amino acid residue, replacing a hydrophobic amino acid residue with a hydrophilic amino acid residue, replacing an acidic amino acid residue with a basic amino acid residue, or replacing a basic amino acid residue with an acidic amino acid residue.

Therefore, modification of a protein of the invention includes any deletion, insertion, addition, replacement or chemical modification of one or more amino acid residue of the protein. Furthermore, Applicants’ specification provides numerous examples of modifications which may be made to create the mutant trichosanthin (MTCS) proteins of the invention. For example, Tables 1, 2, and 3 on pages 7 and 8 of Applicants’ specification provide specific examples of modifications which may be made to the trichosanthin protein. The mutant trichosanthin protein may contain single or multiple modifications. Additional examples of possible modifications to the trichosanthin protein are set forth at page 8, line 8 through page 9, line 8 of Applicants’

specification. Further examples of modification to the trichosanthin proteins and methods for introducing these modifications are set forth at page 11, line 5 through page 11, line 12 of Applicants' specification. Still further examples of MTCS proteins of the invention are set forth at page 12, line 14 through page 19, line 3 of Applicants' specification. Examples 1-22 describe the mutagenesis of trichosanthin proteins to create various MTCS proteins as well as assays for measuring activity of these mutants. Therefore, as set forth above, the scope of the subject matter embraced by the claims is clear and the term "modification" is fully supported by the specification. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection under 35 U.S.C. §112, second paragraph.

Claim 2 has also been rejected under 35 U.S.C. §112, second paragraph. In particular, the Examiner contends that the terms "insertion" and "addition" appear redundant.

Applicants have amended claim 2 to delete the term "addition." Accordingly, the rejection of claim 2 under 35 U.S.C. §112, second paragraph has been rendered moot.

Claim 9 has also been rejected under 35 U.S.C. §112, second paragraph because the Examiner questions the meaning of the term "modified."

Applicants respectfully traverse the foregoing rejection. As set forth above, the term "modification" is defined at page 6, lines 10-22 of the specification and is clear and definite in view of the teachings of Applicants' specification. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

#### **Rejection under 35 U.S.C. § 112, First Paragraph**

Claims 1-11 and 16 have been rejected by the Examiner under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner is of the opinion that "[t]he claims are drawn to a fragment or derivative thereof of a mutant trichosanthin polypeptide. . . The specification does not describe the structure, that is amino

acids in the various polypeptides that can be altered without affecting the function of a specific polypeptide.”

Applicants respectfully submit that based on the teachings in Applicants’ specification, one of ordinary skill in the art would conclude that Applicants were in possession of the claimed invention at the time of filing. However, in an effort to expedite prosecution, and in no way acquiescing to the Examiner’s rejection, claims 1-11 and 16 have been amended such that they are no longer directed to fragments or derivatives of the mutant trichosanthin (MTCS) protein. Accordingly, Applicants respectfully request withdrawal and reconsideration of the foregoing rejection.

#### **Rejections under 35 U.S.C. §102(b)**

Claims 1-4, 8, 9, and 16 were also rejected under 35 U.S.C. § 102(b) as being anticipated by Lee-Huang et al. (U.S. Patent No. 5,532,214). The Examiner contends that Lee-Huang et al. disclose a protein identified as SEQ ID NO:1 which is obtainable from the root tuber of a plant of the genus Trichosanthes. The Examiner further contends that the sequence contains the amino acid sequence of native trichosanthin which contains modifications compared to the claimed fragment or derivative of mutant trichosanthin and that SEQ ID NO:1 of Lee-Huang et al. has 80% local similarity with amino acids 24-68 of the currently claimed mutant trichosanthin. This rejection is respectfully traversed and reconsideration respectfully requested.

SEQ ID NO:1 of Lee-Huang et al. is a polypeptide having a length of 45 amino acids. As amended, claim 1 of the instant application is directed to a mutant trichosanthin (MTCS) protein, comprising the amino acid sequence as set forth in SEQ ID NO:8, with the modification of at least one amino acid residue in the following three regions: amino acid residues 174 to 180, 203 to 226, and 230 to 244. Without acquiescing to the Examiner’s rejection, claim 1, and therefore dependent claims 2-4, 8, 9, and 16, have been amended such that they are no longer directed to fragments or derivatives of the protein set forth as SEQ ID NO:8. The polypeptide disclosed in SEQ ID NO:1 of Lee-Huang et al. does not comprise amino acids 1 to 247 as set forth in SEQ ID NO:8, with the

modification of at least one amino acid residue in the following three regions: amino acid residues 174 to 180, 203 to 226, and 230 to 244. As such, the amino acid sequence of Lee-Huang et al. fails to teach or suggest each and every element of the claimed invention and thus fails to anticipate claims 1-4, 8, 9, and 16. Therefore, applicants respectfully submit that the rejection of claims 1-4, 8, 9, and 16 under 35 U.S.C. §102(b) should be withdrawn.

Claims 1-4, 6, 7, 9, and 16 were also rejected under 35 U.S.C. §102(b) as anticipated by Siegall et al. (U.S. Patent Serial No. 5,541,110). The Examiner contends that Siegall et al. disclose a ribosome-inactivating protein, bryodin 1, having the same biological activities of the native trichosanthin. The Examiner states that the ribosome-inactivating protein identified as SEQ ID NO:2 in Siegall et al. has 60% identity with trichosanthin, and is therefore interpreted as a derivative of the claimed mutant trichosanthin protein. The Examiner further contends that SEQ ID NO:2 of Siegall et al. comprises modifications within amino acid regions 174-180, 196-202, and 203-226. This rejection is respectfully traversed and reconsideration respectfully requested.

As set forth by the Examiner, SEQ ID NO:2 of Siegall et al. is a polypeptide having only 60% identity to the trichosanthin protein. As amended, claim 1 of the instant application is directed to a mutant trichosanthin (MTCS) protein, comprising the amino acid sequence as set forth in SEQ ID NO:8, with the modification of at least one amino acid residue in the following three regions: amino acid residues 174 to 180, 203 to 226, and 230 to 244. Without acquiescing to the Examiner's rejection, claim 1, and therefore dependent claims 2-4, 6, 7, 9, and 16, have been amended such that they no longer encompass fragments and derivatives of the protein set forth in SEQ ID NO:8. The polypeptide disclosed in SEQ ID NO:2 of Siegall et al. does not comprise amino acids 1 to 247 as set forth in SEQ ID NO:8, with the modification of at least one amino acid residue in the following three regions: amino acid residues 174 to 180, 203 to 226, and 230 to 244. As such, the amino acid sequence of Siegall et al. fails to teach or suggest each and every element of the claimed invention and thus fails to anticipate claims 1-4, 6, 7, 9, and 16. Therefore, applicants respectfully

submit that the rejection of claims 1-4, 6, 7, 9, and 16 under 35 U.S.C. §102(b) should be withdrawn.

**Conclusion**

In view of the above, each of the presently pending claims in this application is believed to be in condition for allowance. Accordingly, reconsideration of this application is respectfully requested and the Examiner is respectfully requested to pass this application to issue.

Dated: March 15, 2005

Respectfully submitted,

By Howard M. Frankfort  
Howard M. Frankfort, Ph.D.

Registration No.: 32,613  
DARBY & DARBY P.C.  
P.O. Box 5257  
New York, New York 10150-5257  
(212) 527-7700  
(212) 527-7701 (Fax)  
Attorneys/Agents For Applicant